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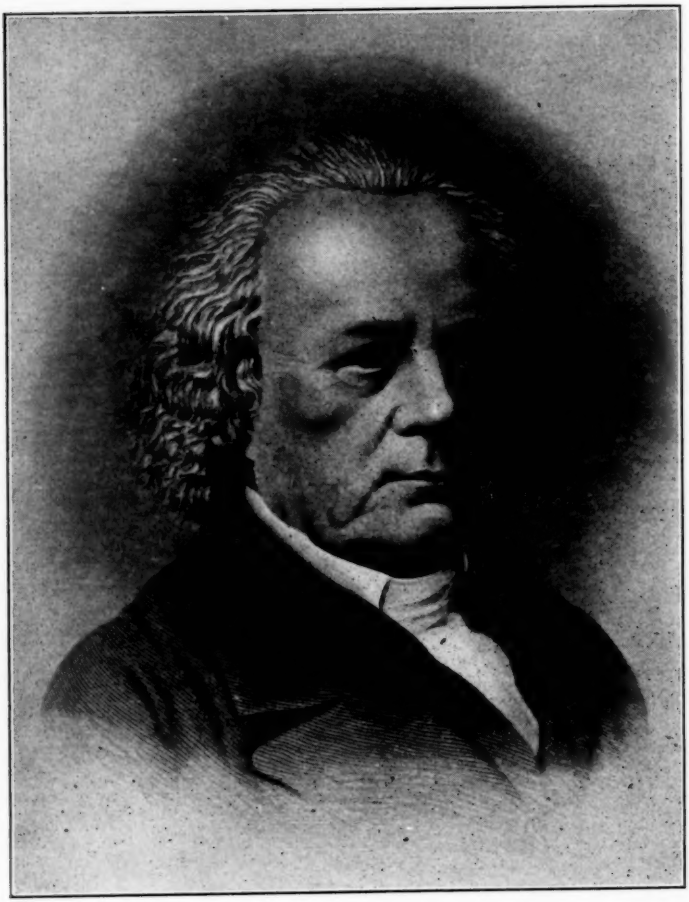

John W. Francis

THE NEW YORK
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VOL. 1 APRIL, 1925 No. 2

JOHN WAKEFIELD FRANCIS (1789–1861)

PRESIDENT OF THE NEW YORK ACADEMY OF MEDICINE (1847–1849)

Of the remarkable group of men who constitute the fine flower of medical New York in the early period, such men as the Bards, John Jones, Wright Post, the elder Hosack, Mitchill, Stearns, Mott, Beck, Alonzo Clark, Willard Parker, Frank H. Hamilton, S. S. Purple, Fisher, and Jacobi, there were none more picturesque than John W. Francis, principal founder and second president of the Academy of Medicine; a sturdy, stocky, benevolent figure of a man, who prided himself on his resemblance to Benjamin Franklin, and who to the last, wore the old-fashioned raiment of Knickerbocker days.

Some ten years ago, Dr. Osler pressed me to write about Francis. I found that his position in the mere general history of medicine could be stated in three lines; for he contributed nothing to scientific medicine and his reputation as a teacher and practitioner was civic and local, an effect of personality. But as a personage he was very remarkable and filled the public eye for half a century. A physician of essentially literary type, he was, in effect the leading practitioner of New York in his day, a kind of medical Mæcenas, at whose house all the visiting celebrities of Europe and America congregated. He inherited his practice in a kind of apostolic succession from Samuel Bard through David Hosack, and was eulogized after his death by Valentine Mott and others in terms that, to-day, seem almost extravagant.

He was born in New York City on November 17, 1789; his mother a Philadelphian of Swiss extraction, his father an immigrant from Nuremberg, a local grocer who, dying of yellow fever

in 1795, left his widow well enough off to educate her son. In the old days, these ethnic associations counted for much, and something of the pleasant Thuringian past hovers about the memory of Francis. Literary aspirations led him to apprentice himself to George Long, a noted publisher of the period, but it was noticed that the boy neglected his dinner to munch an apple under a printing press in pursuit of Latin grammar, and the indentures were soon cancelled by the master. After the usual schooling and private tuition, Francis graduated at Columbia at the age of 20. Two years before he had entered the office of David Hosack. In 1811, when he took his M.D. at the College of Physicians and Surgeons as its first graduate, he was immediately taken into partnership by Hosack, who regarded his junior as the best consultant he had ever known. In 1813, the Medical Department of Columbia College (formerly King's College, founded 1767) was discontinued to fuse with the College of Physicians and Surgeons (founded 1807).

Hosack held the chair of practice, Mott that of surgery, Francis that of materia medica, subsequently, like Nathan Smith, "holding down" other chairs, *viz.*, institutes of medicine, medical jurisprudence and obstetrics. During a visit to Europe, Francis met Byron, Sir Walter Scott, Abernethy, John Bell, Cuvier, Dupuytren, Arago and Geoffroy de St. Hilaire. Abernethy was so taken with him that he invited him to settle in London. Francis was so taken with Abernethy that he copied the eccentric surgeon's dress and offhand traits of speech and manner, "conversational habits" which, we are told, "it cost him, in after years, trouble to discard." In 1826, the whole faculty of the College of Physicians and Surgeons, Francis included, resigned in a body, to join the newly founded Rutgers Medical College. This institution ran under a New Jersey charter although located in New York State. Five years later, legislative enactment closed its doors, and for the next thirty years, Francis devoted himself entirely to medical practice. He had been highly popular as a teacher, but, in the early days, had to eke out his living by writing articles on "Benjamin Rush" and "New York" for Rees' Encyclopaedia, and editing books and journals, of which Denman's Midwifery (1825), gave him considerable kudos and

emolument. By 1820, he was making $15,000 a year. He was essentially charitable and public spirited; his carriage was seen as often in the slums as in Bleecker Street, and his donations to the Historical Society alone amounted to $8,000. When Dewees was dangerously ill, Francis sent a messenger to Philadelphia at his own expense to ascertain his condition. Two pictures in Mott's narrative give us the man. One is that of Francis, bareheaded, following the coffin of a little child (which he had charitably paid for) in an obscure part of the city. The other is the immense gathering of rich and poor alike at his own funeral in the aisles of St. Thomas. "He was," says Mott, "in a very eminent degree, the physician of the poor." His last days were racked by insomnia, gigantic carbuncles, multiple abscesses and spreading aphthae in the throat. His wife, a first class home-maker, looked after his practice, staved off night calls, and kept bores, parasites and promoters at a distance. In the matter of keeping open house, Francis was a kind of Osler. His home at No. 1 Bond Street was frequented in turn by DeWitt Clinton and Daniel Webster, Washington Irving and Fenimore Cooper, Frenea and Bryant, Edmund Kean, George Frederick Cooke and Macready. Astonishing is the number of books, poems, keepsakes and even sheet music dedicated to Francis in his lifetime. Whatever of trash is to be found the catalogue of his library is an index of his innate kindness of heart. He could not resist a book-agent or a canvasser for some pretentious serial publication.

The medical and literary reputation of Francis in our day, attaches to two works: the *American Medical and Philosophical Register* (1810–14), an important periodical which he edited with Hosack, and his anniversary discourse before the New York Historical Society (1857), subsequently reprinted as "Old New York" (1858). The first is a valuable repository of medical cases and biographies of prominent physicians, with hundreds of editorials on all aspects of American life in the period. It contains Francis' case of acute septic peritonitis due to strangulation of the ileum by a Meckel diverticulum complicated by appendicitis, illustrated by a remarkable woodcut. The second is a vivid and readable picture of New York in the first half of

the nineteenth century. Before he died, Francis had been urged to write his autobiography. On his death bed, he said to Mott, "If it had been God's will, I should have been pleased to live a little longer: I should have been satisfied to sit in the chimney corner and write." He wrote countless other things, a collection of pathological cases (1814), on febrile contagion (1816), on cholera (1832), on the mineral waters of Avon (1834), on the anatomy of drunkenness (1841), but nothing quite so good as this book. It contains his often cribbed biography of Mitchill, an extraordinary gallery of old New York clergymen of all denominations, another gallery of contemporary actors and singers, and cultural pictures of all kinds.

Edith Wharton, in "False Dawn" has given a piquant burlesque of the florid, pompous, ponderous, prolix manner of writing and speaking which prevailed in those early days. Alfred Henry Lewis has given us a very liberal dose of it in his novel about Andrew Jackson and Peggy O'Neill. Oliver Wendell Holmes defined it as "chewing the juice out of all the superlatives in the language in Fourth of July orations." Henry James, in "Crapy Cornelia," signalized the later American tendency, to ridicule whatever is not up-to-date and "in the know." The literary manner of Francis combines the two traits. In public speaking, clad in well-fitting but old fashioned clothes, with white neck cloth, he affected the old Abernethian straight-from-the-shoulder manner, "a mountain torrent," "not easy or graceful," Mott says, "convincing if not always persuasive." His literary manner, on the other hand, is often an exaggerated type of that "genteel style of writing" of which Cadogan is the exquisite example in the medical literature of the eighteenth century. The torrent of superlatives would amount to a veritable "geyser of buttermilk," were it not for the deft satiric touch which, in historic retrospect, is plainly the Manhattan or Metropolitan note. As examples of the lapidary, eighteenth century manner: when Francis wants to say that Dr. Mitchill knew many languages and read science extensively, he does it in the funereal manner of Sir Thomas Browne: "Ancient and modern languages were unlocked to him, and a wide range in physical science the pabulum of his intellectual repast." The

complexities of Samuel Parr's wig become "its distensive and seemingly patulous gyrations." Of the sedative effect of the stage on the tired business man, he says: "It proves a wondrous relief to the laborious man and the worn intellect, and is a happy succedaneum for diversions less beneficial to good morals and good health." Chemistry becomes "that science which seems to inosculate with almost every other." And in describing De Witt Clinton's obesity, not content with his own ponderous Johnsonian periods, Francis cites Johnson himself: "an aggravated agglomeration of superabundant redundances." Were this all, our author would be frankly a bore. But read his "Old New York" and you will discover that so excellent is his practical common sense and so striking his wealth of real facts that the florid verbiage is usually humorous in intention. Thus, "Volney's portly form gave outward tokens of his tremendous gastric powers." One clergyman is "a diminutive creature," another "had the bearing of a well-stalled bishop." Old McGrath is "a violent Scotchman" of "captious disposition and unrefined address." Of Mitchill's childlessness, we read: "Like most of our sex, he was married; but, as Old Fuller would say, the only issues of his body were the products of his brain." All admirers of Henry James and Edith Wharton will be reminded here of those demure touches of social satire in which these writers (native New Yorkers both) excel. Francis' book is an essay toward a cultural history of Knickerbocker New York *en profil*. The experienced reader will derive considerable stimulus from the flowing narrative as it dilates successively on the old landmarks, the historic trees, residences, gardens and parks, the faculty and graduates of Columbia College, the clergy, the judiciary, the physicians, the early schools and schoolbooks, the stage, the opera, the painters and sculptors, the clubs, the hospitals, the Academy of Medicine, the Historical Society, the newspapers and magazines and their editors, the native literature, the period, the publishers, the Methodist Book Concern, second only, at that time, to Harper Brothers, and such celebrities as Robert Fulton, Thomas Paine, Edmund Kean and Macready. The musical and dramatic critics have passed him by, but Francis gives page after page about the early actors, about Manuel Garcia (of laryngo-

scope fame) and his daughter Malibran, and about Lorenzo Da Ponte, librettist of Don Giovanni and The Marriage of Figaro. Why, one may ask, has such a worthwhile book been forgotten? The answer is that Francis died on February 8, 1861, just before the Civil War, and the stirring events that followed obliterated his memory except in the minds and hearts of those who, like Jacobi, knew him in the flesh. "Dr. Francis," says his biographer, Gardner, "was essentially a representative man. Many looked upon him as a type of the Knickerbocker settlers of New Amsterdam, with whom it is seen he had no affinity; yet still his short, thick-set frame, which weighed about one hundred and ninety pounds, his straight-bodied coat and vest, his white neckerchief, broad-brimmed hat, inseparable cane and gold spectacles, made a unity in look which fancy associates with the early Dutch settlers." If I may revive some interest in the man and his writings, this sketch will not have been written in vain.

F. H. Garrison.

MODERN COLLOID CHEMISTRY

By Arthur W. Thomas, Ph.D.

(Delivered before the New York Academy of Medicine, February 5, 1925)

Colloids, first classified and named by Thomas Graham (1861); have been considered as a separate and distinct kind of matter, due in part to a misinterpretation of Graham's definition of them. The present trend in the field of colloid chemistry is to regard colloids as individuals or aggregates which when dispersed in a solvent are amenable to the laws governing the conduct of the other state of matter, named "crystalloidal" by Graham for purposes of distinction.

Before discussing the modern trend in colloid chemistry, it would perhaps be helpful to review very briefly the older conception of colloids and colloidal solutions.

Since an irregular translatory and rotational movement (Brownian Movement) was seen in suspensions of particles less than 4 microns ($1\mu = 0.001$ millimeter) in diameter, and

due to the fact that suspended particles were found to migrate in an electrical field, it was believed that colloidal particles remained in solution or suspension by virtue of the Brownian Movement and the repulsive forces arising from the fact that they were electrically charged. In other words, colloidal suspensions were considered to be like clouds.

Colloidal solutions were also considered to be different from ordinary solutions (called "true" solutions as a means of distinction), such as of sodium chloride or cane sugar, in that the colloidal particles could not diffuse through a membrane of parchment paper which was freely permeable to the crystalloids, such as salt or cane sugar. Hence colloidal solutions are generally defined as dispersed systems in which the dispersed phase does not pass through semi-permeable membranes such as parchment, collodion and gut.

Another overworked criterion of colloidality is the optical heterogeneity observed in the ultra microscope.*

Colloidal solutions have also been defined on the basis of the size of the dispersed particles. This has been quite arbitrarily set at larger than 1 millimicron (1 $\mu\mu$ = one-millionth of a millimeter) and smaller than 100 or 200 millimicrons. The upper limit is the limit of the resolving power of the best compound microscope using blue light. This was set at 200 millimicrons by Stoney.[1] The lower limit has no such alibi. It appears to have been adopted from a statement made by Zsigmondy about twenty-five years ago.

In closing this review of the older (and in some circles, the present) ideas concerning colloids, the amorphous appearance of colloids should be mentioned. It is widely believed that there are two worlds of matter, amorphous and crystalline, due to Graham's statement that his colloids were all amorphous. The fact that the substances arrested by the parchment membrane, and which diffused exceedingly slowly through a column of water were amorphous, while those which passed freely through the membrane and diffused readily through water were crystal-

* An ultra microscope is actually just a microscope with orthogonal ultra-illumination.

[1] Stoney: J. Roy. Microscop. Soc. (1903), 564.

line, impressed him so much that he coined the terms *colloid* (glue-like) and *crystalloid*. But he did not mean to imply that colloids were always amorphous as the following quotation[2] will prove—"A similar departure from its normal condition appears to be presented by a colloid holding so high a place in its class as albumen," "In the so-called blood-crystals of Funke, a soft and gelatinous albuminoid body is seen to assume a crystalline contour," "Can any facts more strikingly illustrate the maxim that in nature there are no abrupt transitions, and that distinctions of class are never absolute?"

Anything that appears amorphous is called colloidal as a result of Graham's classification, but many colloids have since been shown to be crystalline. Some proteins may be crystallized and the Debye-Scherrer X-ray method[3] has shown that amorphous looking precipitates consist of amicroscopic crystals.

There are many substances which may exist in solution as "crystalloids" or as "colloids" dependent upon conditions. Colloidal refers, therefore, to a *state* or *condition* of matter, and not to a kind of matter.

The optical heterogeneity observed in the slit ultra microscope, or by use of any of the dark-field illuminators employed in bacteriological technique, is quite commonly believed to be a universal property of colloidal solutions. All colloidal solutions do not show it however, at least with the well known slit ultra microscope or dark-field illuminators using electric arc illumination. The intensity of the diffraction or scattering of light by small particles is a function of several factors as shown in the following expressions,[4]

$$I = K\frac{n\ v^2}{\lambda\ 4}$$

$$I = k\left(\frac{r_{dp}}{r_{dm}} - 1\right)^2$$

[2] Thomas Graham: Phil. Trans. Roy. Soc. *151*, 183 (1861).

[3] Debye and Scherrer: Physikal. Zts. *17*, 277 (1916). Scherrer: Nachr. König. Ges. Wiss. Göttingen (1918), 96.

[4] Lord Rayleigh: Series of papers in Phil. Mag. from 1871 ——.

where I = intensity of scattered light
K = an indeterminate factor depending upon the refractive indices of liquid and dispersed phase, on the amplitude of incident rays and the angle at which the scattered light is observed
n = number of particles in unit volume
v = volume of particles
λ = wave length of light
r_{dp} = refractive index of dispersed phase
r_{dm} = " " " dispersion medium
k = proportionality factor.

It is apparent that unless the indices of refraction of the dispersed phase and of the dispersion medium are quite different, the intensity of the scattered light (or Tyndall Effect) will be very small. This must be so in many colloidal solutions. Gelatin and albumin solutions when thoroughly freed of all foreign matter, and when at hydrogen ion concentrations removed from that of the isoelectric point are optically void in the usual type of ultra microscope. Hence the ultra microscope method is by no means an infallible test for colloidality.*

The use of parchment paper and other semi-permeable membranes has likewise become a poor means of distinction between "colloids" and "crystalloids." The elimination of such membranes as an infallible apparatus for the sifting of "crystalloids" from "colloids" is due to the investigations of Wm. Brown.[5] This investigator showed that semi-permeable membranes vary widely in permeability according to the method of preparation. For example, he prepared membranes which permitted sodium chloride to diffuse through, while arresting the dialysis of sodium chloride. Others were permeable to the colloids, starch and dextrin, while impermeable to the colloidal dye Night Blue, etc. A further interesting study of membranes for use in bacteriological technique has been made recently by Eggerth.[6] The papers by Brown and by Eggerth

* It should be mentioned, however, that when using an exceedingly intense source of light, even chemically homogeneous liquids such as water or benzene scatter light. (*Cf.* Martin: J. Phys. Chem. *26*, 75 (1922).)

[5] Wm. Brown: Biochem, J. *9*, 591 (1915), *11*, 40 (1917).

[6] A. H. Eggerth: J. Biol. Chem. *48*, 203 (1921).

should be studied by all who may have occasion to use such membranes, in dialysis or ultrafiltration.

The Brownian Movement is an effect rather than a cause. It is merely the name applied to the visible manifestation of kinetic energy of the particles or of the molecules of the dispersion medium which are bombarding the particles.

It is natural that prior to the conception of the "Ionic Theory" the motion of colloidal particles in an electrical field was ascribed to electrical charges similar to those on the water particles in clouds. In a given colloidal dispersion all particles migrate in the same direction, consequently they bear the same sign of charge. Since like charged bodies repel each other, it was logical to ascribe the existence of a stable colloidal dispersion to the repulsions of like charged particles opposing the coalescencing influence of gravitational and surface forces.

Smoluchowski[7] points out that such charged suspensions would emit an electrical discharge, like lightning from a cloud, when grounded, as for example, by inserting one's finger into the colloidal solution.

There are many colloidal solutions in which the dispersed phase does not migrate in an electrical field. Examples are proteins at the isoelectric point, starches and dextrins. They are held in solution presumably by the same forces to which the solubilities of cane sugar and common salt are attributed.

The origin of the solution forces and the reason for the electrical migration of colloidal dispersions of apparently insoluble substances such as ferric oxide, antimony sulfide, gold, etc., have gradually become apparent through years of research. It is now definitely known that these insoluble substances do not exist as such in colloidal solution. The particles in colloidal ferric oxide solution consist of a complex of Fe_2O_3 and a soluble iron salt such as $FeCl_3$, antimony sulfide hydrosol consists of a combination between Sb_2S_3 and H_2S. Formulae may be roughly written for them (ignoring the hydrate water) as follows:

$$xFe_2O_3.yFeCl_3 \qquad\qquad xSb_2S_3.yH_2S$$

where x and y are variable and x is always greater than y. When an electrical current is passed through these solutions, a

[7] Z. physikal. Chem. *92*, 129 (1917).

brown precipitate of Fe_2O_3 settles out at the cathode and chlorine is evolved at the anode in the iron oxide hydrosol, while in the antimony sulfide sol, a red deposit of Sb_2S_3 is deposited at the anode and hydrogen gas is liberated at the cathode. This shows that the migrating ions are,—

$xFe_2O_3.yFe^{+++}$	$3y\ Cl^-$
$2yH^+$	$xSb_2S_3yS^=$
To cathode ←	To anode →

The ionization is not complete; it is in fact slight and the migration is not quite so simple as indicated.[8] But it is not possible to make fine distinctions in a short discussion.

The gradual realization of the fact that the "impurities," *e.g.*, the $FeCl_3$ or the H_2S, were essential parts of certain hydrosol particles gave rise to the so-called *Complex Theory*—a very simple statement of the complex nature of certain colloids.

While the Complex Theory was accepted for many colloidal dispersions, hydrosols of noble metals such as gold and platinum were thought to be exceptions, since it was believed that they could be prepared by electrically arcing these metals under pure water. This was disproven by Beans and Eastlack.[9] They demonstrated that colloidal platinum could be formed in pure water due to the fact that platinum oxidizes in the arc, thus generating an electrolyte which became part of the dispersed phase. Gold was shown to require the presence of minute amounts of certain salts, in fact those which form stable chemical compounds of gold.

It is therefore not difficult to see the origin of the solubility forces, since insoluble substances in colloidal solution are actually a part of a complex aggregate containing a soluble component. Evidence for *solution* forces as the reason, or at least one of the reasons for colloid solution stability has been given by Thomas and Frieden.[10] A simple experiment may be cited. Addition of alcohol followed by ether to a hydrosol of xFe_2O_3.

[8] See J. Duclaux: J. Chimie physique *7*, 405 (1909).

[9] Beans and Eastlack: J. Am. Chem. Soc. *37*, 2667 (1915).

[10] A. W. Thomas and A. Frieden: J. Am. Chem. Soc. *45*, 2522 (1923).

$yFeCl_3$ did not affect it. Alcohol promptly precipitated a hydrosol of $xFe_2O_3.yFe_2(SO_4)_3$. Ferric sulfate is insoluble in alcohol.

When a solution of a salt, NaR (or RCl), where Na^+ (or Cl^-) is a diffusible ion and R^- (or R^+) represents a complex nondiffusible ion is placed in solution on one side of a membrane which separates it from an aqueous solution of an electrolyte such as HCl, NaOH, or NaCl, all ions of which are diffusible through the membrane, an unequal distribution of diffusible ions results on the two sides of the membrane. This is the Donnan effect.[11] The sum of the ions of one sign of charge on one side of the membrane will be greater than the sum of the same ions on the other when equilibrium is reached. This gives rise to a difference in potential across the membrane. J. A. Wilson[12] has postulated the existence of a similar orientation of the diffusible ions about a particle in colloidal dispersion. A difference of potential exists between the surface of the particle and the solution in which the particle is suspended. The addition of salts lowers this Donnan potential and at the same time causes the colloidal particles to coalesce and precipitate. Hence the Donnan effect must be considered as an added factor in colloidal stability. It does not apply to electrically neutral colloids such as dextrins where solution forces alone are responsible for the stability.

Magnificent proof of the validity of Donnan's theory, particularly as applied to proteins, has been provided by the late Jacques Loeb.[13] The presentation of Dr. Loeb's point of view will be given by the next speaker.

Application of the method of osmotic pressure for the determination of the molecular weight of colloidally dispersed particles has produced results indicating molecular weights of many thousands. This has been severely criticized by Bancroft[14] who contends that such measurements and deductions are not applicable to heterogeneous systems. Many of the colloidal dispersions investigated by this method certainly show striking evidence of heterogeneity in the ultra microscope.

[11] F. G. Donnan: Zeits. Elektrochemie *15*, 572 (1911).

[12] J. A. Wilson: J. Am. Chem. Soc. *38*, 1982 (1916).

[13] Loeb: Proteins and the Theory of Colloidal Behavior. McGraw-Hill Co., New York, 1925). (Second edition.)

[14] W. D. Bancroft: Applied Colloid Chemistry, page 187. McGraw-Hill Co., New York, 1921.

At the present state of our knowledge of inorganic colloidal dispersions, it is futile to argue this question, while on the other hand, it would appear justifiable to regard certain hydrophilic dispersions as true solutions of large molecules, such as aqueous solutions of albumin, gelatin, Lintner's soluble starch, gum arabic, dextrin, etc.

Such solutions show easily measurable osmotic pressures. As a result, there are numerous published values for the molecular weights of colloids which form hydrophilic dispersions.

Osmotic measurements by W. Biltz[15] and freezing points by Lintner and Düll[16] show the following molecular weights for dextrins:

Achroödextrin	about	2,000
Erythrodextrin	"	3,000
Amylodextrin	"	20,000

Osmotic pressure measurements upon starch solutions by Samec[17] indicate molecular weights of about 100,000.

Published values for molecular weights of many hydrophiles, which exist as compounds of a diffusible with a non-diffusible ion, are, however, of doubtful value in view of the facts developed by Donnan and verified by Loeb.

Osmotic pressure molecular weight determination has been successful with hemoglobin. This is not surprising since the isoelectric point of hemoglobin is practically at the neutral point, *i.e.*, C_{H^+} of 10^{-7} moles per liter. Consequently purification of hemoglobin by dialysis in pure water solution should produce hemoglobin practically free from diffusible ions. By this method the hemoglobin of calves' blood showed a molecular weight of 16,300.[18] It is interesting to compare this figure with those obtained by other methods. Hemoglobin contains iron (0.336 per cent.). Assuming that one atom of iron is contained in one molecule of hemoglobin, a molecular weight of 16,700 is obtained (the accepted value). One gram of calves' hemoglobin combines with 0.00167 gm. of carbon monoxide (Hüfner). Assuming

[15] Z. physik. Chem. *83*, 683 (1913).
[16] Ber. *26*, 2533 (1893), *28*, 1522 (1895).
[17] Samec and Hoefft: Kolloidchem. Beihefte *5*, 195 (1913).
[18] Hüfner and Gansser: Arch. (Anat. u.) Physiol. (1907) 209.

that one mole of hemoglobin combines with one mole of carbon monoxide, a molecular weight of 16,700 is obtained.

Assuming that the hemoglobin molecules are spherical in shape the radius may be calculated from the following formula to be equal to 1.8 millimicrons:

$$M = \frac{4}{3}\pi r^3 d N$$

where M = molecular weight
r = radius of molecules
d = density of hemoglobin molecules in solution (assumed to be a mean of the density of hemoglobin and of water)
N = Avogadro number, 60.6×10^{22}.

The molecular weight of egg albumin dissolved in an ammonium nitrate solution has been indicated to be about 34,000.[19] The "Donnan" effect was allowed for in this measurement.

From its content of tryptophane, casein appears to have a molecular weight of 12,800. The equivalent combining weight[20] of casein for sodium hydroxide multiplied by 6 is 12,600, while the molecular weights obtained by multiplying the values obtained from the sulfur and phosphorus contents by 3 are 12,654 and 13,116, respectively. This is strong evidence that the molecular weight of casein is about 12,700, and that casein is a chemical individual amenable to the classical laws of chemistry, rather than a mysterious agglomerate endowed with the peculiar properties formerly ascribed to colloids.

Mutual Reactions of Colloids

When colloidal solutions are mixed, decrease in stability leading to precipitation may result, or if one of the components of the mixture is a very stable colloid (hydrophilic), and is added in excess while the other is rather unstable (hydrophobic), no visible change may take place and the solution will be found to show the stability and properties of the hydrophilic colloid.

The latter phenomenon is called "protective action." The former case, mutual precipitation of colloids, will be considered first.

[19] Sörensen: Z. physiol. Chem. *106*, 1 (1919).
[20] Cohn and Hendry: J. Gen. Physiol. *5*, 548 (1922–23).

The phenomenon of mutual precipitation of certain colloids was noted by Thomas Graham.[21] Linder and Picton[22] showed that mutually precipitating sols migrated oppositely in an electrical field. This was confirmed by others.

The theory of mutual precipitation, which arose from these findings and from the opinion that colloid stability resided in the mutual repulsion of like-charged particles, was that when oppositely charged colloidal particles are brought together an electrical neutralization ensues resulting in agglomeration of the particles; there being no electrical repulsive forces left, the particles must settle out of solution.

In 1910, Lottermoser[23] suggested that the equivalence may be that of the small amounts of stabilizing electrolyte in the sol, and that the precipitation may be due to a chemical reaction between the stabilizing agents. Experiments with silver ioxide sols indicated that this chemical point of view was correct.

Freundlich and Nathansohn[24] have recently shown that the mixing of pairs of certain like-charged colloids may result in mutual precipitation. For example, they found that arsenic trisulfide hydrosol precipitates Odén's sulfur hydrosol, both of which migrate to the anode in an electrical field. Obviously, the electrical charge neutralization hypothesis fails in this instance. Since Odén's sulfur sol contains pentathionic acid as stabilizing agent (or is one of its stabilizing agents) and arsenious sulfide sol is stabilized by hydrogen sulfide, it was deduced that the mutual precipitation of these sols is a result of the following chemical reaction between their stabilizing agents:

$$5\ H_2S + H_2S_5O_6 \rightarrow 10S + 6\ H_2O$$

Recently a careful quantitative study of mutual precipitation of ferric oxide hydrosol by silica hydrosol has been reported by Thomas and Johnson.[25] This paper offers strong evidence to the effect that mutual precipitation of certain hydrosols is the result of chemical reaction between the ions of the respective stabiliz-

[21] Thomas Graham: J. Chem. Soc. *15*, 246 (1862).
[22] Linder and Picton: J. Chem. Soc. *71*, 586 (1897).
[23] Lottermoser: Kolloid Z. *6*, 78 (1910).
[24] Freundlich and Nathansohn: Kolloid Z. *28*, 258 (1920); *29*, 16 (1921).
[25] Thomas and Johnson: J. Am. Chem. Soc. *45*, 2532 (1923).

ing electrolytes present, to which, in accordance with the "Complex Theory" of colloids, certain colloids owe their stability or solubility forces.

In an extensive series of experiments in which various ferric oxide hydrosols ($xFe_2O_3.yFeCl_3$) were used to precipitate a wide variety of silica sols ($xSiO_2.ySiO_3Na_2$) it was found that the "positive colloid," ferric oxide precipitates the "negative colloid" silica due to chemical reaction between the ferric chloride (or its HCl of hydrolysis) and the sodium silicate (or its NaOH of hydrolysis) quantitatively according to the reaction, $HCl + NaOH \rightarrow NaCl + H_2O$. The mutual removal of the stabilizing agents of both sols by this process of a simple chemical reaction naturally results in the destruction of both colloids.

Thomas and Johnson tried also to study the mutual precipitation of ferric oxide and arsenious sulfide sols as a function of the reaction between the stabilizing ferric chloride of the iron oxide sol and of the stabilizing hydrogen sulfide of the arsenious sulfide sol. The errors existing in the present quantitative methods for the determinations of arsenic and of sulfur are large enough to render an analysis of the $xAs_2S_3.yH_2S$ complex impossible, due to the small amounts involved. In the mutual precipitation of ferric oxide sol and arsenious sulfide sol one of the following reactions may take place: (1) $H_2S + 2FeCl_3 \rightarrow 2FeCl_2 + S + 2HCl$; (2) $3H_2S + 2FeCl_3 \rightarrow 2FeS + S + 4HCl$.

Generally in the precipitation of iron oxide hydrosol by colloidal arsenious sulfide there is no evidence of the latter reaction, since the precipitate is yellow. When, however, the sol contains a large amount of hydrogen sulfide, a blackening develops which can be explained by the formation of ferrous sulfide.

To test the supposition that the mutual precipitation between ferric oxide sol and arsenious sulfide sol is due to the oxidation of the sulfide ion of the stabilizing hydrogen sulfide by the ferric ion of the stabilizing ferric chloride, the following experiment was performed.

Five hundred cc. of an arsenic trisulfide sol was precipitated by a ferric oxide sol, the precipitate dried and extracted with carbon disulfide. SULFUR WAS RECOVERED.

The presence of sulfur in the gel can be accounted for only through the following chemical reaction,

$$S^{=} + 2Fe^{+++} \rightarrow S^{0} + 2Fe^{++}.$$

In view of the evidence submitted by Freundlich and Nathansohn and by Thomas and Johnson, it would appear that the older electrical charge theory of colloid interaction must give way to the chemical reaction hypothesis.

Hydrophilic colloids, such as the proteins, mutually precipitate under certain conditions. It has been shown that protamine[26] precipitates other proteins, and that histone[27] precipitates hemoglobin, serum albumin and globulin. Mutual coagulations between clupein, thymushistone, casein, and hemoglobin have been described by Beth af Ugglas,[28] while Hunter[29] also has contributed to this knowledge.

The significance of the hydrogen-ion concentration of the solution in mutual precipitation of proteins was demonstrated by Michaelis and Davidsohn.[30] They stated that when two amphoteric colloids, such as proteins, are brought together in solution, a compound may be formed and precipitate, the condition for most complete precipitation being a hydrogen-ion concentration between those of the isoelectric points of the reacting ampholytes. Thus when one protein is present as a cation and the other as an anion, the formation of a compound is to be expected, whereas when both proteins are cations (the pH is acid to both of their isoelectric points) or where both are anions (the pH is on the alkaline side of both isoelectric points) a combination between them is not to be expected. The combination between pairs of proteins has resulted in insoluble complexes in practically all cases tried, but since a great deal of work has yet to be done on this subject, it is not safe, at present, to state that proteins always precipitate one another if mixed together at a pH between their isoelectric points. Michaelis and Davidsohn

[26] Kutscher: Z. physiol. Chem. *23*, 117 (1897). Bang: *Ibid.* 27, 483 (1899).

[27] Malengreau: Le Cellule *21*, 121 (1903).

[28] Beth af Ugglas: Biochem. Z. *61*, 469 (1914).

[29] Hunter: Z. physiol. Chem. *53*, 526 (1907).

[30] Michaelis and Davidsohn: Biochem. Z. *39*, 496 (1912).

found also that the optimum pH for the mutual precipitation of proteins varies with the relative amounts of the proteins reacting; when a large excess of one component is present the pH optimum for precipitation will shift toward the isoelectric point of this component.

The precipitation optimum for a mixture of aqueous dispersions of nucleic acid and serum albumin was found to be at pH = 4.05 to 4.22 which is between the isoelectric points of the components, while a mixture of nucleic acid and heat denatured serum albumin precipitated best at pH = 3.8. When the ratio of nucleic acid to the albumin was increased, the optimum reaction for precipitation shifted toward the acid side, *i.e.*, toward the isoelectric point of nucleic acid.

Casein and nucleic acid precipitated each other in a pH range of 4.05 to 2.52 depending upon whether casein or nucleic acid was present in excess. Mixtures of casein with both genuine and denatured serum albumin were found to result in precipitation. Variation in the mass relationships made no difference, due to the fact that the isoelectric points of these proteins are so close together.

Michaelis and Davidsohn[31] investigated the influence of pH in specific precipitations. Using as precipitin the serum of a rabbit that had been previously sensitized with sheep serum, flocculation of this precipitin and sheep serum was obtained equally well at pH = 9 as at pH = 5, thus showing no dependence upon the hydrogen-ion concentration. This sort of reaction is then different from protein mutual precipitation.

De Kruif and Northrup[32] have recently shown the same to be true for the agglutination of *Bacillus typhosus* by immune serum. They found the amount of immune body combined with the organisms is constant from pH = 9 to pH = 3.7 and that the combination is not caused by a difference in sign of the charge carried by the immune body and the organism.

The flocculation of bacteria by proteins, however, has been demonstrated to be similar to protein mutual precipitations.[33]

[31] Michaelis and Davidsohn: Biochem. Z. *47*, 59 (1912).
[32] De Kruif and Northrup: J. Gen. Physiol. *5*, 127 (1922).
[33] Eggerth and Bellows: J. Gen. Physiol. *4*, 669 (1922).

Eggerth and Bellows found that a suspension of *B. coli* is agglutinated by gelatin, crystallized egg albumin, proteoses, edestin and oxyhemoglobin at hydrogen-ion concentrations between the isoelectric point of the protein and the acid flocculation zone of the bacterial suspensions, the latter having been found to lie between pH 1.6 and 3.0.

The proteins of blood serum are precipitated by lecithin suspensions at pH values between the isoelectric points of the reacting substances. The isoelectric points (or pH values for the flocculation optima) of lecithins have been found to vary from pH 2 to 4, depending upon the source.[34] As the proportion of blood serum to lecithin is increased the optimum precipitation tends to shift toward the reaction of the isoelectric point of the blood serum proteins.

An interesting example of the mutual precipitation of hydrophilic or "protective" colloids is that of gelatin with gum arabic. This gum appears to consist mainly of the calcium salt of a complex carbohydrate acid. In view of the work of Jacques Loeb, one would expect a precipitation of gelatin by gum arabic in solutions on the acid side of pH 4.7 (the isoelectric point of gelatin) provided gelatin arabate is an insoluble compound.

Thomas Graham showed that gelatin is precipitated by "gummic acid," the coagulum settling out to form a jelly-like mass. This has been rediscovered by Tiebackx,[35] whose attention to it was aroused by the fact that oil-in-water emulsions "broke" upon mixing if one was emulsified with gum arabic and if gelatin was the emulsifying agent in the other one. He found that gelatin and gum arabic mutually precipitate in a solution sufficiently acid to ensure the presence of gelatin cations, the coagulum setting to a jelly when warmed. In the presence of an excess of gelatin this precipitation does not occur. This is an example of the "protective" effect of an excess of one of the hydrophilic components. Tiebackx also noted that gum tragacanth precipitates gelatin.

Protective Action

When a solution of a hydrophilic colloid is added to a less stable colloidal dispersion, or suspension, generally there is no

[34] Feinschmidt: Biochem. Z. *38*, 244 (1912).

[35] Tiebackx: Kolloid Z. *8*, 198, 238 (1911); *31*; 102 (1922).

change in appearance of the system and the less stable dispersion is found to have become more stable, *i.e.*, it is no longer so sensitive toward coagulation by either the addition of electrolytes or by evaporation to dryness. The less stable dispersion is said to have been "protected" by the hydrophilic colloids such as gelatin, gum arabic, albumin, etc.

The discovery of protective action may be attributed to Michael Faraday who noted that the addition of gelatin to his colloidal gold dispersions rendered them so stable that it was possible to evaporate them to dryness without change in color.[36]

Since there appears to be a general tendency to regard "protective" colloids as a class that always confers increased stability upon lyophobic colloids, it would be well to stop for a moment in order to show that "protective" colloids do not differ so radically from others in their conduct in mutual reactions. It is more a difference in degree than in kind. For example, hydrophilic colloids may precipitate other dispersions. A number of instances have just been cited where certain protective colloids precipitate each other.

The precipitation of alumina hydrosol by "protective" gelatin was observed by Thomas Graham. This appears to have been overlooked since in recent colloid literature one notes reports of the discovery that protective colloids occasionally do not protect. One such report is that of Brossa and Freundlich.[37] These authors find that the addition of a small amount of well dialyzed albumin solution to ferric oxide hydrosol renders the latter more sensitive toward the precipitating influence of electrolytes, rather than more stable. The explanation for this is simple, and will be returned to later.

Protective colloids may protect less stable dispersions or may render them still less stable, even resulting in mutual precipitation depending upon the signs of the charges* of the protector and hydrophobe, and upon the relative proportions of the two sols brought together. The significance of the signs of the charges carried by the two colloids interacting was shown by

[36] Phil. Trans. *147*, 184 (1857).

[37] Brossa and Freundlich: Z. physik. Chem. *89*, 306 (1915).

* Ionic charges.

Billitzer,[38] who noted that a solution of gelatin which contains a trace of acid will precipitate arsenious sulfide sol, while when a negative charge is conferred upon the gelatin by addition of a very small amount of ammonium hydroxide, it will then mutually precipitate with ferric oxide sol. If, however, a slightly positive gelatin is mixed with the ferric oxide sol, protection takes place. The complex is not precipitated by the addition of a slight amount of ammonium hydroxide but the sign of the charge of the complex is changed from positive to negative.

In view of the modern chemistry of protein solutions, and the envelope theory of protection enunciated by Bechhold,[39] an explanation is available. The solution of gelatin in dilute ammonium hydroxide contains not only ammonium and gelatinate ions but also ammonium hydroxide and its ionization products, *i.e.*, ammonium gelatinate hydrolyzes in aqueous solution. The stability of ferric oxide sol is due to the ferric chloride, or acetate, as the case may be, that is combined with the ferric oxide particles. When these two sols are mixed the ammonium hydroxide and ferric chloride or acetate react to form hydrous ferric oxide. If the condition of "isoelectric" proportions of the interacting sols obtains, then precipitation ensues due to the removal of all of the stabilizing agent of the ferric oxide sol, and due to the fact that there is not sufficient gelatin present to "protect" it, *i.e.*, to form envelopes around the ferric oxide particles and thus keep the latter in dispersion through the solution forces of the gelatin. It must be noted as well that gelatin at or near its isoelectric point (hydrogen-ion concentration at which its ionization is at a minimum), is much less stable in solution than in the presence of acid or alkali, as shown by Jacques Loeb.

On the other hand, when the inorganic colloid is present in large excess, the neutralization or the removal of a part of its stabilizing agent is not sufficient to throw it out of solution, while in the case of a large excess of oppositely charged gelatin, no precipitation ensues due to the enveloping of the "neutral-

[38] Billitzer: Z. physik. Chem. *51*, 129 (1905).
[39] Bechhold: Z. physik. Chem. *48*, 385 (1904).

ized'' inorganic colloid particles by gelatin, which by reason of its solution forces maintains the ''neutralized'' particles in suspension. The sign of the charge depends simply upon whether gelatin cations or anions are present, *i.e.*, whether it is an acidic or alkaline solution.

Hence when Billitzer mixed gelatin, ammonium hydroxide and ferric oxide sol in the order named, it is easily seen why he got flocculation. When he mixed acidified gelatin, ferric oxide sol and ammonium hydroxide he did not get flocculation of the mixture because gelatin films had formed around the ferric oxide particles. Addition of ammonia merely changed the envelopes of cationic gelatin to gelatin anions. Had he, however, added the base slowly he would have noted a point of very low stability of the gelatin-enveloped ferric oxide particles, namely at pH = 4.7, the isoelectric point of this protein.

The sensitizing action of well dialyzed albumin (Brossa and Freundlich) upon ferric oxide hydrosol can be explained similarly since, in neutral aqueous solution this protein is on the alkaline side of its isoelectric point, *i.e.*, it is negatively charged (anionic) and forms salts with the ferric ion of the stabilizing ferric salt, or causes hydrolysis of the latter due to its combination with the hydrochloric or acetic acid in hydrolytic equilibrium with the stabilizing ferric salt of the ferric oxide hydrosol.

To summarize, a hydrophilic colloid will protect a less stable dispersion at all concentrations of the former provided its sign of charge is like that of the latter. If it carries a charge of opposite sign, it will protect the less stable dispersion if an amount in excess of the isoelectric mixture is present. If added in amounts such as to give an isoelectric mixture or less than the same then the stability of the less stable dispersion will be decreased, possibly resulting in precipitation.

Various hydrophilic colloids show different protective effects, as revealed by the well known ''gold number'' method of Zsigmondy.[40] The ''gold numbers'' are useful solely as very rough indices of relative protective powers, because the ''gold number'' of a given ''protective'' colloid depends so largely upon many

[40] Zsigmondy: Z. anal. Chem. *40*, 697 (1901).

conditions which limits of time and space prohibit discussing here.

Attempts have been made to apply the gold number method to analysis of urines. The presence of protective substances in urines have been found,[41] but it is doubtful whether the method can have any diagnostic value. Ottenstein[42] has been unable to find characteristic gold numbers in urines from certain pathological cases. He notes that the gold number of the well dialyzed solids of normal urines ranges from 3.5 to 7.0 while in disease, fluctuating values are found both above and below the "normal" values and not at all characteristic for any one pathological condition.

The envelope mechanism of protective action has been quite definitely proven by Jacques Loeb[43] by a comparison of the stability of protein solutions with that of dispersions of protein-coated collodion particles.

A small quantity of an aqueous collodion suspension was placed in contact with an aqueous solution of a protein. The particles were centrifuged from the protein solution and made up to a creamy suspension in water at a desired pH. This suspension of protein-coated particles was added to various salt solutions to note the behavior. The effects of various salts were followed by electrophoresis measurements and observation of the concentrations of a given electrolyte which caused precipitation. It was found that the conduct of the protein-coated particles is identical to that of a solution of the protein. The concentrations of different salts required to precipitate suspensions of gelatin-coated collodion particles in water are practically identical with the concentrations of the same salts required to "salt out" gelatin from aqueous solutions. Furthermore, he found that just as the solubility of gelatin at its isoelectric point (pH = 4.7) is increased by the addition of certain kinds and amounts of salts, isoelectric gelatin-coated collodion particles are rendered more stable in an identical manner.

[41] Lichtwitz and Rosenbach: Z. physiol. Chem. *61*, 112 (1909); Lichtwitz: *Ibid.* *64*, 144 (1910); Salkowsky: Berlin klin. Wochenschr. (1905).

[42] Ottenstein: Biochem. Z. *128*, 382 (1922).

[43] Jacques Loeb: J. Gen. Physiol. *5*, 479 (1923).

Loeb noted a peculiar behavior in the case of egg albumin. He found that it is not a good protective colloid for collodion suspensions. Investigation of the properties of albumin-coated collodion particles showed them to be practically identical in stability to that of suspensions of denatured (heat coagulated) albumin particles. He postulated that when egg albumin forms a film of its solution about collodion particles, the albumin molecule undergoes a rearrangement or orientation to render its water soluble groups ineffective.

Loeb also found casein and edestin to be poor protectors for collodion particles. He defined protective colloids as follows:

"Protective colloids must be capable of forming a durable film on the surface of suspended particles and the molecules constituting the film must have a higher attraction for the molecules of the solvent than for each other; in other words, they must possess true solubility. Only in this case can they prevent the precipitating action of low concentrations of electrolytes on particles which are kept in suspension solely by the high potentials of an electrical double layer. Thus gelatin films, in which the attraction of the molecules for water is preserved, have a general protective action, while crystalline egg albumin, casein, and edestin, which seem to lose their attraction for water when forming a film, have a protective action only under limited conditions . . ."

In conclusion, it may be stated that modern colloid chemistry emphasizes chemistry. Colloid chemistry is the chemistry of solutions or dispersions of practically non-diffusible dispersed phases. This is not new; it was the basis of Graham's origination of colloid science but was forgotten until so vigorously revived by Loeb.

Since colloidal particles are practically non-diffusible they are chemical individuals of very high molecular weight, or consist of a large number of low molecular weight molecules adhering together forming a heavy aggregate.

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THE APPLICATION OF MODERN CONCEPTS OF COLLOIDAL CHEMISTRY TO MEDICINE

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(From the Department of Medicine, College of Physicians and Surgeons, Columbia University and the Presbyterian Hospital, New York. Delivered before the New York Academy of Medicine, February 5, 1925.)

I

Perhaps the most important rôle of science in the history of civilization has been the substitution of a simple physical and chemical explanation of the phenomena of nature for that shroud of superstition and mysticism which for centuries retarded the advance of human knowledge. In the application of these physical and chemical laws to the explanation of vital processes certain difficulties have been encountered. These difficulties have in part resulted from the fact that the proteins and certain other colloids which are important constituents of protoplasm do not appear to obey the laws which apply to other substances. In order to surmount these difficulties, a new and special chemistry has been developed. Pioneer workers in the field of colloidal chemistry have attempted to explain the phenomena which they observed on the basis of this special chemistry, the theories of which are complicated and at variance with the usual laws of chemistry. Recent investigation has shown, however, that there is in fact nothing mysterious about these colloids and that they also obey the laws of classical chemistry when the conditions of the experiment are properly controlled. I shall try this evening to trace as simply as possible the development of colloidal chemistry, and to show that the modern concepts in this branch of chemistry promise to reveal the cause of many hitherto perplexing biological phenomena. As the time allotted to me is short, my discussion will be limited entirely to the proteins.

II

In 1861 Thomas Graham first proposed a distinction between crystalloids and colloids. According to him these two groups of substances differ in three important respects. First, crystal-

loids have a tendency to separate out of solution as crystals, and colloids as a rule separate out in amorphous or glue-like masses. Second, crystalloids diffuse readily through certain membranes (parchment, pig's bladder and collodion), whereas these same membranes are very slightly if at all permeable for colloids. Finally, colloids exist in solution in a condition of "physical aggregation," whereas crystalloids do not show this characteristic, *i.e.*, they are present in molecular form. These distinctions, as made by Graham, mark the beginning of so-called colloidal chemistry, which were it not for precedent might be more appropriately termed the physical chemistry of the colloidal state, for many crystalloids may possess colloidal properties under appropriate conditions.

Soon after Graham distinguished between crystalloids and colloids, the property of aggregation came to be considered of paramount importance and the lack of diffusibility of the particles (termed by Naegeli micellae or crumbs) was considered of only secondary significance. It would have been more fortunate for colloidal chemistry had the emphasis been placed upon the difference in diffusibility between crystalloids and colloids, for the recent work of Jacques Loeb has shown that many of the colloidal properties of proteins can be entirely and satisfactorily explained as a result of this difference.

However, to explain the properties of swelling, osmotic pressure, changes in viscosity and precipitation or flocculation of proteins, the adsorption theory was developed. This theory is based upon the idea that the particles of proteins are not in molecular solution but that they are present in clumps of molecules, which are impermeable for the solution. Hence it was thought that the true molecular reactions of classical chemistry could not take place between these clumps and electrolytes in the solution, and that all reactions must consequently occur only at the surface of the clumps. This meant that the proteins would not obey the law of multiple proportions and other familiar laws of chemistry. In order to explain the extraordinary reactions of colloids a purely empirical formula was developed by Freundlich. While certain reactions could be accounted for by this formula, it was found to hold only within

certain very narrow limits. On the basis of the adsorption hypothesis many of the reactions were at first considered to be physical in nature. Later Bugarszky and Liebermann, Pauli, and others came to believe that the reactions of proteins were purely chemical but that ions were "adsorbed" preferentially by the proteins. This idea was developed by W. B. Hardy and later by Perrin, who suggested that the proteins adsorbed hydrogen ions in acid solution and OH ions in alkaline solution, because in acid solution particles migrated to the cathode in an electrical field, whereas in alkaline solution they migrated to the anode. At a point near neutrality no migration occurred and this point was termed the isoelectric point. It was observed that precipitation of proteins was greatest at the isoelectric point, whereas osmotic pressure and swelling were at a minimum, and it was assumed that this was due to the fact that charges on the particles had been "annihilated" by an ion of opposite charge, thereby permitting the suspended particles to coalesce. The adsorption theory seemed in accordance with the old findings of Hofmeister that various ions even with the same valence had different effects on properties such as swelling, osmotic pressure and viscosity. Alterations in viscosity, osmotic pressure and swelling brought about by salts, acids and alkalis were assumed by Pauli and Ostwald to be due to the fact that protein molecules or micellae were surrounded by jackets of water, these being greatest in certain concentrations of acids and alkalis, being lessened by the addition of salt and being at a minimum at the isoelectric point where no shell of water was thought to be present. There was no experimental evidence for this view yet it constitutes the well known hydration theory of colloids upon which theories of edema have been built. That this hypothesis of hydration of the proteins is superfluous will be shown later.

The further colloidal chemistry developed, the more vague and unwieldy it became, because the adsorption theory had practically no quantitative data for its support, and because the truly colloidal phenomena of swelling or osmotic pressure, viscosity and precipitation were confused with purely molecular phenomena of solubility, cohesion, adhesion and surface tension. which form a part of the physics of the electron.

That a great state of confusion did exist, and that no correlation of the great mass of data accumulated in chemical and biological science was possible, may be seen from the words of Zsigmondy, a leader among the colloidal chemists. He states that " . . . no general theory of colloids can be given, for the study of colloids has become a great and extensive science in the development of which many must assist; only when the . . . material has been properly systematized will a theory of colloidal solutions be raised from *mere consideration of the similarities in special cases to the standing of an exact science.*"

III

A turning point in the history of modern colloidal chemistry was the development of simple methods for the determination of hydrogen-ion concentrations by Sörensen, Michaelis, and Clark, for it was by the application of these methods that Jacques Loeb was able to prove his contention made in 1904 that proteins are highly hydrolyzed amphoteric electrolytes which probably obey the familiar laws of classical chemistry, and therefore that no new chemistry need be developed to explain colloidal phenomena.

In 1917 Loeb began his studies of the proteins. His first important contribution was the discovery that when the pH of the solution is controlled, proteins combine with acids and bases exactly as do other amphoteric electrolytes. For example, it takes three times as much $\frac{N}{10}$ H_3 PO_4 to bring an isoelectric protein to pH of three as it does of $\frac{N}{10}$ HCl or $\frac{N}{10}$ HNO_3 for at this range of pH H_3 PO_4 acts as a monobasic acid and therefore only one of the three hydrogen ions is active. It was also shown that a protein combines only with acids on the acid side of its isoelectric point forming salts of the type of protein chloride or sulphate and it combines only with bases on the alkaline side of its isoelectric point forming metal proteinates such as sodium proteinate. These observations showed that the assumption of adsorption was quite unnecessary. Furthermore, these results showed that the aggregates which may be present

in a protein solution react with electrolytes as though they were individual molecules in solution, in contrast to the idea of masses in which surface forces alone are responsible for reactions.

The next step taken to disprove the adsorption theory was to show that the weird Hofmeister series of ion effects largely disappeared when the pH was controlled and differences in solubility were eliminated. Thus it became clear that apparently only the *valency* of the ion with a charge opposite to that of the protein was of significance in influencing colloidal behavior.

The final step necessary to disprove the adsorption theory was to find some mathematical expression which would account for the colloidal behavior of proteins. This revealed itself in the so-called Donnan equilibrium. In 1911 Donnan showed that when a membrane separates two solutions of electrolytes (and the principle holds only for electrolytes) one of which contains an ion which can not pass through the membrane, the result will be an unequal distribution of the diffusible ions on the two sides of the membrane. This unequal concentration of the crystalloidal ions must give rise to osmotic forces and to differences in electrical potential between the two solutions separated by the membrane. In almost innumerable experiments, in which potential differences have been determined simultaneously with the changes in the colloidal properties, Loeb and his coworkers have shown that these forces explain the colloidal behavior of proteins.

At the isoelectric point of a protein, colloidal properties are at a minimum, as is the potential difference, because here there is no ionization of the protein; therefore no Donnan equilibrium is established and consequently electrolytes distribute themselves equally on both sides of the membrane. Upon the addition of a small amount of acid or alkali, the protein is ionized, a Donnan equilibrium is established and colloidal properties are seen to be at a maximum, for here the concentration of crystalloidal ions is greater in the protein solution than in the outside solution free from protein. Upon the further addition of an acid or alkali, or of a neutral salt, the colloidal properties again diminish, as does the potential difference between the protein

solution and its watery environment, for here the P.D. is depressed by the ion of opposite sign of the protein. The higher the valency of the oppositely charged ion, the greater the depressing effect.

So much for the theories of colloidal behavior. Had the older colloidal chemists had the advantage of the more recent investigations, theories of edema like that of Martin Fischer, which for some years stimulated clinicians to use therapeutic measures, perhaps not entirely rational, would not have received serious consideration.

IV

In the last chapter of the second edition of his book on "Proteins and Theory of Colloidal Behavior," Loeb says:

"Life phenomena cannot be dissociated from colloidal behavior and the idea of an organism or of living matter consisting exclusively or chiefly of crystalloidal material, or of material with purely crystalloidal behavior, is inconceivable. Organisms have been defined as chemical machines consisting essentially of colloidal material capable of growing and automatically reproducing themselves. If this be true, advance in general physiology will be chiefly a hit or miss game until science is in possession of a mathematical theory of the colloidal behavior of the substances of which living matter is composed. If Donnan's theory of membrane equilibria furnishes the mathematical and quantitative basis for a theory of colloidal behavior of the proteins, as the writer believes it does, it may be predicted that this theory will become one of the foundations on which modern physiology will have to rest."

Only a few years have elapsed since this statement was made but in this short time there have been distinct advances based on the newer concepts of colloidal chemistry. The following examples taken from various fields of biological science will serve to illustrate this point.

The factors determining the digestion of proteins by pepsin have for years puzzled physiological chemists and as Sörensen has indicated, many observations and theories were contradictory largely because of the failure to measure the hydrogen-ion concentration of the solutions employed. No thorough under-

standing of the factors involved in the action of pepsin was possible until the chemistry of the proteins upon which it acts, was thoroughly understood. Since this has been made possible, Northrop has systematically restudied the problem with the result that pepsin action is now quite understandable and has been shown to follow the laws of classical chemistry, the assumption of adsorption by the protein, or its cleavage products, being unnecessary. He has shown that pepsin acts largely or entirely on ionized protein, as suggested by Nasse, Pauli and Euler, and that the degree of aggregation (*i.e.*, whether the protein be in solution or precipitated) makes no difference. Furthermore, he has shown that apparent deviations from the law of mass action, which were thought to be due to adsorption, result merely from an equilibrium between pepsin and the peptone formed in the process of digestion, and that the substance so formed also follows the usual laws of chemistry. Northrop has extended his study to trypsin digestion with equal success, though the problem is somewhat more complex.

In the realm of immunology, possibly more than elsewhere, a state of turmoil has existed as a result of lack of understanding of the chemistry of proteins, but that there are better times ahead may be surmised from Gideon Wells's statement that "such studies as those of Jacques Loeb on the behavior of protein solutions bid fair to throw *more* light into the knowledge of immunity than most of the *direct* investigations of immunological problems."

Northrop and De Kruif have approached the problem of agglutination by a study of the stability of bacterial suspensions and their results have been in part well summarized by Shibley, who says:

"According to these writers agglutination may be considered in terms of two antagonistic forces, a *repelling* force which keeps the bacteria apart, due to like charge on the bacteria, and a cohesive or sticking force, which is probably a function of surface tension. In any bacterial suspension these forces may be thought of as opposed to each other; greater relative repelling force making for stability, and greater relative cohesive force leading to flocculation. They have shown, in the case of both

unsensitized and sensitized bacteria, that agglutination takes place as soon as the potential is reduced (by electrolytes) to a critical zone lying between about −15 and +15 millivolts, provided the cohesive force is unaffected; that is, the cohesive force then becomes relatively greater than the repelling force. They have shown in the case of unsensitized bacteria, that salt in high concentration (over 0.01 N) reduces the cohesive force and, at the same time, narrows the critical potential agglutination zone; but that in the case of sensitized bacteria such reduction of cohesive force and of potential agglutination zone does not take place. And they have furthermore found that all electrolytes tested in low concentration (less than 0.01 to 0.1 N) affect primarily the potential, while in concentration greater than this, the effect is principally on the cohesive force."

Shibley, working at the Presbyterian Hospital, has extended these studies to the phenomenon of spontaneous agglutination of streptococci, and finds that this apparently occurs when the cohesive forces are higher than those usually present in salt solutions commonly employed as electrolyte in specific agglutination reactions. He has also shown that immune agglutinating sera possess a specific charge-reducing substance which is quantitatively related to the agglutination titer of the serum, and that in absorption experiments this substance is lost. Highly protective but non-agglutinating sera cause no diminution in electrical charge.

At the Presbyterian Hospital, Dr. Palmer, Dr. Atchley and I have been interested in the study of edema. We have made simultaneous analyses of blood serum and edema fluids (from the chest or abdomen) taken from patients suffering from nephritis, cirrhosis, cardiac disease and tuberculous pleurisy. These analyses showed certain constant features. Regardless of the cause of edema, whether the fluid be exudate or transudate, it was found that the Cl concentration in the edema fluid was always higher than that of the blood serum, that the K content of the blood serum was greater than that of the fluid, that the sodium, bicarbonate, sugar and urea, were equally distributed between both. In view of the recent application of the Donnan equilibrium to the chemistry of proteins it seemed that this might be the cause of the unequal distribution of

potassium and chlorine between the blood serum and edema fluid. To test this, blood serum was separated from the corresponding edema fluid by a collodion membrane and the system was allowed to come to equilibrium. Analyses of the serum and edema fluid were again made and the discrepancies, before noted, persisted. Thus evidence was found that blood serum and edema fluid are in equilibrium as though they were separated in vivo by a collodion membrane, and that the equilibrium is probably a manifestation of that described by Donnan.

Recently Van Slyke, Wu and McLean have made an intensive study of the factors controlling the electrolyte and water distribution in the blood. First, they studied the relations determining equilibria between red blood cells and the serum in which they are bathed. Then they studied the equilibria between blood serum and tissue fluid. They have found that if we assume that three laws holding for dilute solutions also hold for blood (one of these being the Donnan equilibrium), then, mathematical expressions can be deprived which will predict the distribution of electrolytes between cells and serum.

From this brief resumé, it may be seen that the modern concepts of protein chemistry have already greatly enhanced our understanding of enzyme action, of agglutination and of water balance in the body. All three of these mechanisms are, of course, decidedly important to the clinician.

In conclusion, I should like to say a few words regarding the relation of medicine to purely physico-chemical study of the type presented this evening. It is the function of the physician to treat disease, but to do this successfully he must know its cause. This has been axiomatic since the days when Hippocrates taught his followers that disease was a part of the course of nature, rather than the product of supernatural influences. To understand the abnormal, we must naturally have clearly in mind the laws governing normal function or physiology. To understand normal function we must be able to measure quantitatively those physical and chemical forces by which it is controlled, and we must furthermore be able to predict mathematically what changes will take place under various conditions. Towards the accomplishment of this end, the modern concepts of protein chemistry appear to be of great significance.

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The National Union List of Serials

The Library of the New York Academy of Medicine has recently joined the ranks of libraries cooperating in the publication of a national union list of serials. The term serial, as applied to the holdings of the Library of the Academy, includes medical journals in all languages; transactions of medical and other scientific societies, local, national and foreign; reports of hospitals, clinics and social welfare institutions and organizations; and publications of colleges and universities in this country and abroad that have appeared or are appearing in periodical form.

When this work of listing and recording the holdings of the cooperating libraries is complete, the results will be put in printed form and distributed to the libraries as a "provisional list." This list will be used as a basis of exchange and as a "want" list among the cooperating libraries, which will thus be enabled to complete imperfect sets or to acquire new ones by purchase or exchange. Such changes and additions will be recorded in the "provisional list," which will then be returned to the publishers in charge of the work, the H. W. Wilson Company, of New York City, and a permanent list will then be printed and distributed for use in the various libraries.

This final list will be of great value, not only to the individual libraries as a bibliography of their periodical material, but to the whole field of medical, scientific and research work. For it will be, first, a bibliography in alphabetic form of all important

serial publications, both defunct and current, in the various countries of the world. Moreover, under each entry will be indicated just what sets, complete or otherwise, are to be found in the cooperating libraries of the United States and Canada. This means that a vast field of material in these libraries will be made available for use and consultation to readers and workers in the many different fields represented by the libraries, which are both general and special in scope.

The large and valuable collection of medical periodicals and other serial publications on related scientific subjects in the Library of the Academy of Medicine is now being recorded and entered in this union list. The result will be that its value and usefulness will be manifoldly increased and augmented by being made available to the whole field of medicine in America. This is the first time in history that a union list of serials has been compiled on a national basis, so the work is a vast and complex one; but the undertaking will more than justify all effort by its tremendous significance as a definite step toward the scientific organization and rendering available for practicable use of the vast but widely separated sources of scientific, technical and literary material in the libraries of North America.

Regulations Governing Donations to the Library Funds, Adopted by the Council of the Academy, January 28, 1925

"Donations and bequests are solicited by The New York Academy of Medicine for the maintenance and expansion of the Library.

"A donation or bequest of $5,000 or more will provide for a special library fund, the income of which may be used for the general purposes of the Library or restricted to the purchase of books and periodicals, as the donor or testator may indicate. When so restricted, a special bookplate will be used. A donation or bequest of less than $5,000 but more than $1,000 will provide for a named library fund, the income of which will be used for general library purposes or restricted for the purchase of books and periodicals, as desired by the donor or testator.

"Donations of less than $1,000 will be added to the general library funds."

The Library will be glad to receive books, journals, pamphlets and reprints which Fellows or their friends do not need. Upon notification either by post or telephone, our expressman will call for them.

The borrower's convenience is greatly enhanced by his being allowed to take out an unlimited number of reprints. He is thus not affected by the rule which permits but five books to be taken out at one time. Also the free use of pamphlets saves much wear and tear on the bindings of books. The constant demand for bound volumes of the leading journals has resulted in so much deterioration that they have been withdrawn from circulation. However, through various donations most of these journals are complete in duplicate and may be borrowed.

Each reprint is catalogued both by author and subject, and a member may select what he needs from the subject catalogue, by simply indicating the author and the number on a bit of scratch paper.

Brown 98765
Jones 41144
Robinson 606, etc.

THE NEED OF HOSPITAL PROVISION FOR CHRONIC PATIENTS

More people die from chronic diseases than from acute. The proportion would undoubtedly be even much higher than the mortality statistics indicate, if every death certificate were carefully made out and showed the chronic disease which is largely responsible for the fatal result as well as the immediate cause of death or the terminal condition. For example, a patient with neurosyphilis and an involvement of the liver, heart and kidneys whose death is immediately due to static pneumonia may be reported as having died of "pneumonia," if the physician does not care to report beyond that. No extensive morbidity statistics are available to supplement our knowledge of the prevalence of chronic illness.

The problem of "the chronic" has been characterized as a challenge to the medical profession, and some day this challenge will have to be met.

The out-patient departments of the hospitals are filled with people of the poorer classes who seek relief from some distressing or incapacitating chronic ailment. Their needs are met to some extent in this department of the hospital but it is difficult to give them adequate attention under present conditions. There is, however, a very large group of patients for whom a visit to the dispensary and a bottle of medicine can do very little unless it is accompanied by a carefully supervised regimen of rest and diet, or perhaps some form of physiotherapy for a prolonged period. Very few of the poorer classes, if any, are able to secure this at home and the hospitals will not take them. A few convalescent homes will open their doors to them but they can only stay for a few weeks—so brief a sojourn may benefit a patient convalescing from an acute condition, but for the chronic sufferer it is scarcely long enough to exert any appreciable influence. Moreover very few convalescent homes are prepared to give the careful medical supervision and scientific study which is so frequently needed if a patient with a chronic disease or condition is to improve or to be restored to economic usefulness.

Since the general and special hospitals are concerned chiefly with the care of the acutely ill, and the convalescent homes, with one or two exceptions, are not equipped to care for the chronic, special institutions for their care and study seem to be necessary if progress is to be made in this long neglected field. The need of institutions of this type is well recognized. Proprietary institutions endeavor to fill the need of those who can afford to pay but the facilities for people of small income are almost nil.

The sufferers from the various rheumatic diseases; from cardiac and vascular troubles of various kinds and degrees; those with mucous colitis, and other gastro-enteric diseases who can not carry out the required mode of life in their homes; those with affections of the neuromuscular system; with leg ulcers; renal affections; orthopedic cases, and many others require the facilities of special institutions. These are very limited in New York City, and with a single exception, unsatisfactory. They were established chiefly to provide custodial care for chronic

conditions that have reached the incurable stage, and the medical attention usually provided is of an indifferent character. What is urgently needed are hospitals for the care of those who have not yet advanced to this hopeless state. Active medical work of high grade will mean the salvaging of many of these men and women afflicted with ailments generically and dismally known as chronic.

The municipality recognizes its obligation in the matter and maintains in its hospitals many patients who are chronically ill, but in City Homes (or Almshouses) and at the Central Neurological Hospital only advanced or custodial cases are admitted. Consideration is now being given to the question of devoting one of the existing municipal hospitals for the types of cases described above. The Public Health Committee of the Academy of Medicine has conferred with Mr. Bird S. Coler, Commissioner of the Department of Public Welfare, concerning the matter and has enlisted his active interest. One institution may not be enough, but this is a matter which experience will determine. Private philanthropy may supplement the municipal endeavor as it has so nobly done in the case of tuberculosis sanatoria. The latter, if the hope for further reduction of tuberculosis is realized, may be turned over for the care of other types of reclaimable sufferers from chronic diseases.

Only men interested in the study and treatment of chronic diseases should be appointed to the medical staffs of these institutions, if these are to function properly. Competent resident staffs and proper nursing are also essential, and the equipment should include all the known therapeutic resources. Boas, Rappleye and others have called attention to the need of study of the progress of chronic diseases, and these hospitals when properly manned will offer an opportunity for such study.

When proper attention is given to the treatment of chronic ailments, the charlatans' field for exploitation will rapidly shrink. At present it is this class of patients who are the prey of unscrupulous healers of many cults.

E. H. L–C

REVIEWS OF THE HOSPITAL SITUATION IN GREATER NEW YORK

The report on "The Hospital Situation in Greater New York" was published late in 1924 in book form by G. P. Putnam's Sons, 2 West 45th Street, New York. It is based on a comprehensive survey of hospital conditions, by a special staff of workers under the direction of Dr. E. H. Lewinski-Corwin, the Executive Secretary of the Public Health Committee, who studied the administrative, medical and nursing procedures of the hospitals and the numerous relationships between the hospitals and the community. The following review published in "The Hospital and Health Review" of London, December, 1924, is one of many illustrating the wide recognition and endorsement which the report has received here and abroad.

"The interest and value of this report to the British reader lie not in the fact that it is what it purports to be, a survey of the hospitals in New York, though that would invest it with both those qualities for many, but that, by reason of the breadth of view with which the topics dealt with are treated, it is very much more. It might well be described as a systematic and comprehensive general study of important hospital questions. The range of subjects of which it treats is so wide, the manner in which each in turn is approached, investigated and discussed is so admirable in its soundness, orderliness and thoroughness; in short, the whole book, alike in matter and method, is so excellent and of so wide an application that we strongly recommend it. It is worthy not only of perusal but of study by everyone who takes an interest in hospital questions. Certainly no hospital administrator, be he committeeman or official, should fail to give it thoughtful study.

It begins, or rather would begin if the reader were to take our advice and read chapter 3 first, with a consideration of the problem of illness among the people, the extent and character of disease, the determining of the illness rate, and the question of the place of the hospital in the treatment of disease. This, in particular, has an application to all places, and is not pertinent merely to New York or even the United States. This chapter is, perhaps, to the British reader, the most interesting of any in the book, inasmuch as it demonstrates the practicability of determining on substantial grounds the relation which the numerical strength of hospital beds should bear to population.

Other chapters treat of revenue and expenditure, concluding with a consideration of surpluses and deficits; administration; medical organization; nursing, including the scarcity of nurses, which prevails in New York as in London—an excellent chapter; hospital records; convalescents; special problems; and community problems, embracing the mutual responsibility of the community to hospitals and hospitals to the community.

It is impossible to comment in detail on the contents of this most valuable treatise—a considerable volume might profitably be devoted to such a purpose. It will, however, perhaps surprise many to learn that, whereas in London, with its population of 7,250,000, the hospitals included in the Statistical Report of King Edward's Fund number 116, contain 12,660 beds, and cost, in round figures, to maintain, £2,630,000; the hospitals in Greater New York, with a population of 5,620,000, number 182, contain 32,000 beds, and cost to maintain $35,000,000—say, £7,000,000 at par of exchange. The Public Health Committee of the New York Academy of Medicine who publish this survey consists of 33 doctors whose time is occupied for the greater part of the year, and who were assisted during most of this time by a special staff of four physicians, three nurses, three social workers, and two accountants. It is quite as interesting and almost as valuable to the Briton as to the citizen of the United States."

REPORT OF THE COMMITTEE ON MEDICAL EDUCATION

At a joint meeting of the Society for the Advancement of Clinical Information and the New York Association for Medical Education, held October 18, 1923, it was resolved that if the Academy of Medicine concurred, the work of the two organizations should be joined together under the direction of a Committee on Medical Education of the Academy. A resolution was adopted by the Council of the Academy at its meeting in December approving this action. A Committee on Medical Education was thereafter appointed, consisting of the members of the former governing bodies of the two organizations who were Fellows of the Academy, and an Executive Committee with Dr. Charles N. Dowd as chairman.

The activities which the Committee decided upon to take up at once were much the same as those which were announced and carried on by the two organizations which had just been merged. They included plans for the maintenance of a bureau where information in detail should be kept of all graduate opportunities offered in Greater New York, as well as elsewhere in the United States and in foreign countries; this information to be made available for medical men who might make inquiry in person or by letter. Contact with the courses as carried on was to be kept up, in order that the Committee might be advised of the manner in which they were conducted, the qualifications of the teachers, the adequacy of the material and equipment, and so forth. The need of additional special internships or residencies for training in the specialties was to be made a subject for study.

Sub-committees were appointed composed of Fellows of the Academy generally recognized as specially qualified in their particular subjects, to investigate and report upon courses offered in New York. These sub-committees have been actively engaged in the work and with one or two exceptions have already presented their reports.

Based upon these reports synopses have been prepared showing the opportunities for graduate medical study offered in New York in each of the clinical specialties. The sub-committees are made up as follows:

Medicine	Dr. Walter L. Niles, Chairman
	Dr. Emanuel Libman
	Dr. Samuel A. Brown
	Dr. Charles N. B. Camac
Surgery	Dr. Eugene H. Pool, Chairman
	Dr. Emil Goetsch
	Dr. Henry H. M. Lyle
Neurology	Dr. Frederick Tilney, Chairman
	Dr. Foster Kennedy
	Dr. Charles A. Elsberg
Psychiatry	Dr. Thomas W. Salmon, Chairman
	Dr. Menas S. Gregory
	Dr. George H. Kirby
Obstetrics	Dr. George Gray Ward, Chairman
&	Dr. Howard G. Taylor
Gynecology	Dr. William E. Studdiford
Ophthalmology	Dr. James F. McKernon, Chairman
&	Dr. Arnold H. Knapp
Oto-Laryngology	Dr. Cornelius G. Coakley

Public Health	Dr. Haven Emerson, Chairman Dr. William H. Park
Pediatrics	Dr. Rowland G. Freeman, Chairman Dr. Charles Hendee Smith Dr. Oscar M. Schloss
Urology	Dr. Edward L. Keyes, Chairman Dr. J. Bentley Squier Dr. Alfred T. Osgood
Orthopedic Surgery	Dr. Reginald H. Sayre, Chairman Dr. Leo Mayer
Dermatology & Syphilology	Dr. John A. Fordyce, Chairman Dr. Howard Fox Dr. Hans J. Schwartz
Psychiatry	Dr. Thomas W. Salmon, Chairman Dr. Geo. H. Kirby Dr. Menas S. Gregory
Roentgenology	Dr. Jos. M. Steiner Dr. Ross Golden Dr. Harry M. Imboden Dr. Leopold Jaches

The subject of special internships or residencies which are available in New York is now being studied by the Committee. Approved opportunities of this nature will be announced in the synopses in connection with the courses which are offered.

The daily Bulletin of Surgical Clinics has been published daily throughout the year. There has been a considerable increase in the number of hospitals, surgeons and operations posted in the Bulletin. The daily average for 1924 has been

Hospitals	29
Operations, etc.	171
Surgeons	89

The Weekly Bulletin of Medical Clinics posts especially arranged clinics, given at 24 different hospitals. Five hospital services announce a clinic once a month; six, twice a month; one, three times a month; ten, once a week; and two, four times a week or oftener.

The Bureau of Clinical Information posts a list of the fixed clinics of the city. The Bureau aims to furnish information to visiting medical men in regard to courses, lectures, and clinics, and other medical activities of the city.

A total of 436 visitors have called at the Bureau of Clinical Information during the year 1924. They have registered from

every country of Western Europe except Portugal; Russia, Czecho-Slovakia, Armenia; China, Japan, India, Ceylon, Formosa, Australia, South Africa; Argentina, Brazil, Colombia, Chile, Venezuela, Panama, Hawaii, the Philippines, Canada, from coast to coast, and from every state in the Union.

During the year the bureau has gathered much information as to graduate medical work in England and on the Continent. This is being added to and kept up to date through the courtesy of the officials of a number of international agencies, fellowships and societies, and particularly of American medical men returning from a period of study abroad.

LIST OF APPROVED OPPORTUNITIES FOR GRADUATE MEDICAL STUDY OFFERED IN NEW YORK CITY

DERMATOLOGY-SYPHILOLOGY

Columbia University.
Advanced course of 2 yrs.
Group of 7 short courses.
Cornell University Medical College.
1 clinical course.
Post Graduate Medical School & Hosp.
Assistantship in clinic.
Skin and Cancer Hospital.
Special internship.
Montefiore Hospital.
Special internship.
Brooklyn Hospitals.
2 extension courses.

INTERNAL MEDICINE

Columbia University.
6 weeks practical course, full day.
Group of 15 short courses.
Post Graduate Medical School & Hosp.
3 months seminar of full days work.
19 special courses.
Beth Israel Hospital.
Course in Cardiology.
Brooklyn Hospitals.
32 extension courses.
Special Internships.
3 in Mt. Sinai Hospital.
1 in Montefiore Hospital.
4 in Bellevue Hospital.

NEUROLOGY AND PSYCHIATRY

Columbia University.
Group of 16 courses.
Neurological Institute.
Post graduate clerkship.
Post Graduate Medical School & Hosp.
2 special courses.
Cornell University.
3 short courses.
Brooklyn Hospitals.
3 extension courses.
Special Internships.
2 in Bellevue Hospital.
1 in Mt. Sinai Hospital.
1 in Montefiore Hospital.

OBSTETRICS AND GYNECOLOGY

OBSTETRICS

Lying-In Hospital.
2 courses.
Post Graduate Medical School & Hosp.
Manikin course.
Brooklyn Hospitals.
7 extension courses.

GYNECOLOGY

Post Graduate Medical School & Hosp.
1 months seminar, full days work.
8 special courses.
Columbia University.
2 short courses at Mt. Sinai Hospital.
Brooklyn Hospitals.
3 extension courses.

Special Internships in Obs. & Gyn.
8 in Lying-In Hospital.
4 in Woman's Hospital.
1 in Nursery & Child's Hospital.
1 in Manhattan Maternity Hospital.
5 in Long Island College Hospital.
3 in Berwind Maternity Clinic.
1 in Harlem Hospital.
1 in Mt. Sinai Hospital.
1 in Roosevelt Hospital.
1 in Brooklyn Hospital.
9 in Sloane Hospital for Women.
9 in Bellevue Hospital.
2 in Community Hospital.
1 in Bronx Maternity Hospital.
3 in Jewish Maternity Hospital.
1 in Brooklyn Hebrew Maternity Hosp.
1 in N. Y. Foundling & St. Ann's Mat. Hosp.

OPHTHALMOLOGY

Herman Knapp Memorial Hospital.
8 months comprehensive course.
Post Graduate Medical School & Hosp.
7 months comprehensive course.
11 special courses. 5 internships.
Manhattan Ear, Eye & Throat Hosp.
Combined 9 months course in Ophthalmology and Oto-laryngology.
4 internships in Ophthalmology.
New York Eye and Ear Infirmary.
9 special courses. 1 internship.
Brooklyn Eye and Ear Hospital.
Clinical course.
Brooklyn Hospitals.
4 extension courses.
Mount Sinai Hospital.
1 internship in Ophthalmology and Oto-laryngology.
Bellevue Hospital.
3 internships.

OTO-LARYNGOLOGY

Columbia University.
6 months comprehensive course.
4 internships in Bellevue Hospital.
Post Graduate Medical School & Hosp.
Seminar of 3 full time courses of 3 months each.
16 special courses. 4 internships.
Manhattan Eye, Ear & Throat Hospital.
Combined 9 mos. course in Ophthalmology and Oto-laryngology.
6 internships.
New York Eye and Ear Infirmary.
6 special courses. 1 internship.
Brooklyn Eye and Ear Hospital.
4 special and clinical courses.
Brooklyn Hospitals.
3 extension courses.
Mt. Sinai Hospital.
1 internship in Ophthalmology and Oto-laryngology.

ORTHOPEDIC SURGERY

Post Graduate Medical School & Hosp.
2 months seminar of full days work.
10 special courses.
Brooklyn Hospitals.
4 extension courses.
Special Internships.
6 in Hospital for Ruptured and Crippled.
7 in Hospital for Joint Diseases.
1 in New York Orthopedic Hospital.
1 in Montefiore Home.

PEDIATRICS

Columbia University.
2 months course of full days work.
Group of six-weeks courses.
Post Graduate Medical School & Hosp.
6 months course of full days work.
15 special courses.
Brooklyn Hospitals.
12 extension courses.
Pediatric Interships.
6 in Bellevue Hospital.
4 in Babies' Hospital.
3 in St. Mary's Free Hosp. for Children.
1 in Nursery & Child's Hospital.
3 in N. Y. Infirmary for Women and Children.
1 in Mount Sinai Hospital.
2 in N. Y. Foundling & St. Ann's Mat. Hosp.
2 in Presbyterian Hospital.
2 in Lenox Hill Hospital.
1 in Post Graduate Hospital.

SURGERY

Univ. & Bellevue Hosp. Medical College.
3 years comprehensive course.

Columbia University.
6 weeks course in general surgery at New York Hospital.
Group of 5 courses at Mt. Sinai Hosp.
Course in surgery technique. Operative surgery on animals.
Post Graduate Medical School & Hosp.
Seminar in general surgery, full day.
4 special courses. 7 special courses in operative surgery.
Brooklyn Hospitals.
16 extension courses.
Special Internships.
1 in Post Graduate Hospital.
4 in Mt. Sinai Hospital.
1 in Montefiore Hospital.
2 in Skin and Cancer Hospital.
3 in New York Hospital.
5 in Bellevue Hospital.

UROLOGY
Post Graduate Medical School & Hosp.
6 special courses.
New York Hospital.
1 six months course. 1 special internship.
Roosevelt Hospital.
1 private course. 1 special internship.
Brooklyn Hospitals.
4 extension courses.
Bellevue Hospital.
2 internships.

STATUS OF THE NEW BUILDING, MARCH 20th, 1925

The Carnegie Corporation has appropriated $1,550,000 for the new building. It is expected that the building can be completed for less than that sum. The Council of the Academy is of the opinion that there will be a sufficient sum remaining from the sale of the old building to pay for the furniture and equipment of the new building.

The floor plans and facade have been approved by the Building Committee, the Council, and the Carnegie Corporation. Working drawings are being pushed to a conclusion.

The contract for steel has been let. Excavation and foundation should be finished by the time steel arrives, which will be in the month of July. The building should take approximately a year and a half for completion after steel begins to go up. The Fellows of the Academy may expect to get into the new building in 1927.

Messrs. York & Sawyer are the architects, Mr. Frank Sutton is Consulting Engineer, and Messrs. Marc Eidlitz & Son, Inc., are the contractors.

DEATHS OF FELLOWS OF THE ACADEMY SINCE JANUARY 1st, 1925

MORRIS HAROLD FRANTZ, 48 East 61st Street, New York City; born in Kiel, Russia, June 10, 1891; graduated from the Homeopathic Medical College, New York City, 1915; elected a Fellow of the Academy December, 1924; died January 19, 1925. Dr. Frantz was a member of the American Society for the Advancement of Science. He was assistant attending neurologist at the City Hospital, attending neurologist at St. Vincent's Hospital, Staten Island, associate neurologist at the Post Graduate Dispensary, and assistant in the dispensary of the Neurological Institute.

WILLIAM MCKAY, 33 East 24th Street, New York City; born in Ontario, Canada, March 7, 1850; graduated in medicine from the University of Toronto, 1878; elected a Fellow of the Academy October 3, 1889; died January 8, 1925.

WALTER M. SILLECK, 445 Park Avenue, New York City; born in New York City, April 15, 1883; graduated from the College of Physicians and Surgeons in 1908; elected a Fellow of the Academy March 6, 1919; died February 15, 1925. Dr. Silleck was a Fellow of the American Medical Association and of the American College of Surgeons. He was associate visiting surgeon at the Post Graduate Medical School and Hospital, and assistant surgeon at the Harlem Hospital.

JOHN W. SMALL, 40 Depeyster Street, North Tarrytown, New York; born in Bowdoinham, Maine, June 5, 1849; graduated from Bowdoin Medical College, Maine, in 1871; elected a Fellow of the Academy January 2, 1890; died February 21, 1925.

WILLIAM E. PORTER, 41 West 73rd Street, New York City; graduated from the College of Physicians and Surgeons, New York City, 1888; elected a Fellow of the Academy December 3, 1891; died March 26, 1925. Dr. Porter was a Fellow of the American Medical Association.

JOHN JAMES COTTER, 204 West 70th Street, New York City; born in New Bedford, Mass., August 3, 1869; graduated from the College of Physicians and Surgeons, New York City, 1898; elected a Fellow of the Academy February 3, 1921; died February 11, 1925. Dr. Cotter was a Fellow of the American Medical Association. He was associate laryngologist at the Hospital for Ruptured and Crippled, and assistant otologist and laryngologist at the Vanderbilt Clinic.

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